2. Restriction Requirement

Applicant hereby confirms their election of the claims of Group I, namely claims 1-24 and 28. Applicant has, therefore, cancelled claims 25-27 and 29-56 as being drawn to a non-elected invention but reserves their right to pursue these claims in a divisional application.

3. Information Disclosure Statement

The Examiner has indicated that the Information Disclosure Statement filed on March 14, 2001 fails to comply with the rules because the Fuller et al. (1998) reference was not present with the application. Applicant has enclosed a copy of the Fuller et al. (1998) reference with their response and requests that the information therein be considered on the merits.

4. Claim Objections

The Examiner has objected to the claims 1-24 and 28 because they refer to the non-elected invention. The Examiner has also objected to claims 8-14, 16-24 and 28 as being improper multiple dependent claims. Applicant has amended the claims to address these issues and believes that the amendments have obviated the objection. Reconsideration and removal of the objections is, therefore, requested.

5. Claim Rejections under 35 U.S.C. §112

A. Enablement

The Examiner has rejected claims 1-24 and 28 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Applicant respectfully traverses. The present invention is directed to a method of treating various disorders (e.g. osteoporosis) through active immunization by targeting autologous OPGL. The

Specification discloses a number of art-recognized methods for breaking auto-tolerance to self-proteins and a person of ordinary skill in the art could practice the full scope of the invention without any undue experimentation.

The Examiner's specific comments with respect to the alleged lack of enablement are set forth in the paragraphs numbered 11-16 of the Office Action (see pages 7-9). Applicant has responded to each of the Examiner's comments on an item-by-item basis as follows:

i) Paragraph 11

In paragraph 11 of the Office Action, the Examiner has argued that the teachings of the prior art would cause a person of ordinary skill in the art to doubt that the claimed method would work. For example, the Examiner asserts that specific biological actions/activities would be affected by the immunogenic peptide and that one might expect antibodies to interfere with the osteoclasts. The Examiner argues that the Specification does not provide guidance on how to overcome these expected obstacles. Applicant respectfully disagrees.

The concept of peptide and polypeptide vaccination against self-proteins is well known in the art of immunology. The effects obtained through immunization with vaccines that target self-proteins have also been well documented. Today, most autovaccines in clinical trials are peptide vaccines, *i.e.* vaccines containing a single defined B-cell epitope of a self-protein which is coupled or fused to an immunogenic carrier moiety or a strong T-cell epitope. Once administered, the antibody-bound self-proteins may be simply cleaved by scavenger cells and/or they may be further inactivated due to interaction with a functional site in the self-protein. Regardless, both of these effects lead to a down-regulation of activity. This should be self-evident when the antibodies produced are inactivating. Clearing of proteins would similarly lead to a fall in the concentration of the targeted self-protein whereby the activity of the self-protein would be down-regulated (*see, for example*, the paragraph bridging pages 11-12 of the Specification).

The down-regulation of OPGL is, therefore, not a mystery. If OPGL reactive antibodies are raised and the antibody titer is sufficiently high, then the antibodies will be able to induce a reduction in OPGL activity (either by neutralization or by simple clearance).

ii) Paragraph 12

In paragraph 12, the Examiner comments on the modification of the polypeptide and argues that the Applicant has failed to provide enough direction or guidance within the Specification to enable the skilled artisan to make and/or use the claimed invention. Applicant respectfully disagrees. When amino acid variations are introduced into a native polypeptide sequence, it almost certainly results in an immunogenic mutant or variant in certain parts of the population. The introduction of an amino acid change will with high probability give rise to amino acid sequences that include the change which are also capable of binding MHC Class II molecules in some haplotypes, and this will, therefore, result in breaking of autotolerance. So, the concept of rendering a self-protein immunogenic will not pose a problem for the skilled artisan.

Although the Examiner is correct when he states that the functionality of a protein may be altered by even a single point mutation, this concept is not particularly relevant in the instant case. It is often desirable to destroy the biological activity of a protein when one is devising a variant of the biologically active self-protein. And, it should be self-evident that a vaccine containing a single B-cell epitope coupled to an immunogenic carrier stands no chance of being biologically active. These types of peptide vaccines are well-known in the art.

Applicant submits that the claims are enabled because the Specification teaches various methods of breaking autotolerance. The Specification teaches how to modify and obtain useful polypeptides to practice the invention. The Examiner's attention is specifically directed to pages 20-28 of the Specification which describe the preferred use of promiscuous epitopes as well as the use of traditional carrier proteins such as KLH, tetanus toxoid and diphtheria toxoid to accomplish this purpose.

iii) Paragraphs 13 and 14

In paragraph 13, the Examiner argues that the Specification does not address how regulation may be affected by the claimed invention. The Examiner cites to three articles which describe the "unpredictability" of the effects of regulation of function. In paragraph 14, the

Examiner comments on analogs and how even minor alterations to protein structure can have an unpredictable affect on its function. The Examiner further states that a large quantity of experimentation would be necessary to identify all the functional analogues of SEQ ID NO. 2 and that the Specification fails to provide any direction/guidance regarding synthesizing, screening and evaluating these non-peptide analogues.

Applicant would like to point out that the concept of down-regulation is defined in the paragraph bridging pages 11 and 12 of the Specification. Although the general definition of "regulation" might relate to intracellular events, "down-regulation" in the present context is simply defined as a reduction in OPGL binding to its receptors. This concept is set forth in the claims and is supported by the disclosure in the Specification.

With respect to the Examiner's comments in paragraph 14, it should be noted that claim 1 as amended specifically defines what is meant by an analogue (a peptide structure that includes at least one B-cell epitope from OPGL and at least one modification). Numerous routine methods of identifying B-cell epitopes from a protein are known in the art (see, e.g., page 14 of the Specification which describes the use of monoclonal antibodies for epitope mapping). Computer programs and algorithms also exist and are widely used in the art to identify linear epitopes. As such, Applicant submits that the Specification does define what constitutes an analogue and that methods of synthesizing, screening and evaluating non-peptide analogues would be within the knowledge of a person of ordinary skill in the art and would only require routine experimentation.

iv) Paragraph 15

In paragraph 15, the Examiner argues that amino acid substitutions, deletions, additions can result in mutations, the effects of which may be unknown. The Examiner further argues that undue experimentation would be required to evaluate all possible effects of mutation on peptide formation and that the Specification does not describe or teach which specific mutations in the codons are to be acted upon, etc. As can be seen in amended claim 1, the OPGL polypeptide analogue having the general formula 1 requires that the immunogen include a subsequence of OPGL that includes a B-cell epitope. Therefore, the claimed constructs do not encompass any frameshift mutations. Secondly, as explained above in sections (i) and (ii), any mutation will as

a rule give rise to an increase in immunogenicity in at least some individuals and hence result in the breaking of autotolerance, the desired objective.

v) Paragraph 16

Finally in paragraph 16, the Examiner argues that the Applicant has failed to establish a nexus between the immunogenic modified peptide administered to the animal as recited in the claims and the production of specific and effective self anti-OPGL antibodies that down-regulate osteoprotegerin as recited in the claims. Applicant respectfully disagrees. As discussed in the Specification and as detailed above, the binding of antibodies to autologous OPGL will down-regulate OPGL by means of inactivation and/or clearance.

The foregoing remarks demonstrate that the claimed invention is fully described and enabled by the Specification. The Specification discloses a number of art-recognized methods for breaking auto-tolerance to self-proteins. A person of ordinary skill in the art could identify and select OPGL analogues useful for practicing the invention in view of the Specification's teachings and the general knowledge in the art. As such, Applicant respectfully submits that a person of ordinary skill in the art could practice the full scope of the invention without any undue experimentation.

B. Indefiniteness

The Examiner has also rejected claims 1-7, 11-12, 15, 18-19 and 24 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner specifically states that the method claims are incomplete, claim 15 lacks antecedent basis support for the limitation "cytokine" and claims 1, 22 and 28 improperly use the phrases " including" and "such as". Applicant has amended the claims to remove the phrases "such as" and "including" and has included new dependent claims with the removed subject matter. Applicant has also amended the method claims to more clearly define the invention and has cancelled claim 15 thereby rendering the rejections moot. Reconsideration and removal of the rejections is respectfully requested.

Favorable consideration and early allowance of the claims is requested.

If the Examiner has any questions concerning this application, the Examiner is requested to contact the undersigned at 714-708-8555 in Costa Mesa, CA.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), applicant(s) hereby petition(s) for an extension of time for two (2) month(s) to April 1, 2003 for filing a reply to the Office Action dated November 1, 2003 in connection with the above-identified application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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3631-0108P

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner of Patents and Trademarks, Washington D.C. 20231 on: April 1, 2003
(Date of deposit)

BIRCH, STEWART, KOLASCH & BIRCH, LLP

Susan M. Farquharson
(Signature)

April 1, 2003
(Date of Signature)

CLAIMS

1. (Currently Amended) A method for *in vivo* down-regulation of osteoprotegerin ligand (OPGL) activity in an animal~~, including a human being~~, the method comprising effecting presentation to the animal's immune system of an immunogenically effective amount of

~~at least one OPGL polypeptide or subsequence thereof which has been formulated so that immunization of the animal with the OPGL polypeptide or subsequence thereof induces production of antibodies against the OPGL polypeptide, and/or~~

~~at least one OPGL analogue wherein is introduced at least one modification in the OPGL amino acid sequence which has as a result that immunization of the animal with the analogue induces production of antibodies against the OPGL polypeptide,~~ an OPGL polypeptide analogue having general formula I:

$$(MOD_1)_{s1}(OPGL_{e1})_{n1}(MOD_2)_{s2}(OPGL_{e2})_{n2}....(MOD_x)_{sx}(OPGL_{ex})_{nx}$$

-where $OPGL_{e1}$-$OPGL_{ex}$ are x B-cell epitope containing subsequences of OPGL which independently are identical or non-identical and which optionally contain foreign side groups, x is an integer ≥ 3, n1-nx are x integers ≥ 0 of which at least one is ≥ 1, $MOD_1$-$MOD_x$ are x modifications introduced between the preserved B-cell epitopes, and $s_1$-$s_x$ are x integers ≥ 0 of which at least one is ≥ 1 if no optional side groups are introduced in the $OPGL_e$ sequences, whereby the animal's own OPGL is down-regulated due to binding thereof to ~~the~~ antibodies induced by immunization with the OPGL polypeptide analogue,

OPGL being a protein which acts as an osteoclast differentiation factor and which has an amino acid sequence as set forth in SEQ ID NO: 2 for human OPGL and in SEQ ID NOs: 4 and 6 for murine OPGL.

2. (Cancelled).

3. (Currently Amended) The method according to claim ~~2~~1, wherein the analogue comprises ~~modification has as a result that a substantial fraction of OPGL B-cell epitopes are preserved and that~~

~~at least one foreign T helper lymphocyte epitope ($T_H$ epitope). is introduced, and/or~~

~~at least one first moiety is introduced which effects targeting of the modified molecule to an antigen presenting cell (APC) or a B-lymphocyte, and/or~~

~~at least one second moiety is introduced which stimulates the immune system, and/or~~

~~at least one third moiety is introduced which optimizes presentation of the modified OPGL polypeptide to the immune system.~~

4. (Cancelled).

5. (Currently Amended) The method according to claim ~~3 or 4~~1, wherein the ~~modification~~ OPGL polypeptide analogue includes an amino acid substitution in ~~and/~~or deletion in ~~and/~~or insertion in ~~and/~~or addition to the OPGL polypeptide sequence, or any combination thereof.

6. (Cancelled)

7. (Cancelled)

8. (Currently Amended) The method according to ~~any one of claims 2-7~~claim 1, wherein the ~~modification~~ OPGL polypeptide analogue includes a duplication of at least one OPGL B-cell epitope ~~and/or introduction of a hapten~~.

9. (Currently Amended) The method according to ~~any one of claims 3-8~~claim 3, wherein the foreign T-cell epitope is immunodominant in the animal.

10. (Currently Amended) The method according to ~~any one of claims 3-9~~claim 9, wherein the foreign T-cell epitope is capable of binding to a large proportion of MHC Class II molecules.

11. (Original) The method according to claim 10, wherein the at least one foreign T-cell epitope is selected from a natural T-cell epitope and an artificial MHC-II binding peptide sequence.

12. (Currently Amended) The method according to claim 11, wherein the natural T-cell epitope is selected from a Tetanus toxoid epitope [such as P2 or P30 (SEQ ID NOs: 34 and 35,

respectively)], a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope, and a *P. falciparum* CS epitope.

13. (Cancelled)

14. (Cancelled)

15. (Cancelled)

16. (Cancelled)

17. (Currently Amended) The method according to ~~any one of the preceding claims~~claim 1, wherein the OPGL polypeptide analogue~~or subsequence thereof has been modified~~ contains a modification ~~in any one of positions 170-192, any one of positions 198-218, any one of positions 221-246, any one of positions 256-261, or in any one of positions 285-316, the amino acid numbering conforming with that of any one of SEQ ID NOs: 4, 6, and 12, or wherein the OPGL polypeptide has been modified~~ in any one of positions 171-193, any one of positions 199-219, any one of positions 222-247, any one of positions 257-262, or in any one of positions 286-317, the amino acid numbering conforming with that of SEQ ID NO: 2.

18. (Original) The method according to claim 17, wherein the modification comprises a substitution of at least one amino acid sequence within a position defined in claim 17 with an amino acid sequence of equal or different length which contains a foreign $T_H$ epitope.

19. (Currently Amended) The method according to claim 18, wherein the amino acid sequence containing the foreign $T_H$ epitope substitutes ~~amino acids 256-261 and/or 288-302 and/or 221-241 found in SEQ ID NO: 4 or~~ amino acids 257-262 and/or 289-303 and/or 222-243 in SEQ ID NO: 2 or in a polypeptide where a cysteine corresponding to Cys-221 of SEQ ID NO: 2 has been substituted with Ser.

20. (Currently Amended) The method according to ~~any one of the preceding claims~~claim 1, wherein presentation to the immune system is effected by having at least two copies of the OPGL polypeptide analogue~~, the subsequence thereof or the modified OPGL polypeptide~~ covalently of non-covalently linked to a carrier molecule capable of effecting presentation of multiple copies of antigenic determinants.

21. (Currently Amended) The method according to ~~any the preceding claims~~ claim 1, wherein the OPGL polypeptide~~, the subsequence thereof, or the modified OPGL polypeptide~~ analogue has been formulated with an adjuvant which facilitates breaking of autotolerance to autoantigens.

22. (Currently Amended) The method according to ~~any one of the preceding claims~~claim 1, wherein an effective amount of the OPGL polypeptide ~~or the OPGL~~ analogue is administered to the animal via a route selected from the parenteral route ~~such as~~selected from the group consisting of ~~the intradermal, the subdermal,~~ the intracutaneous, the subcutaneous, and the intramuscular routes; the peritoneal route; the oral route; the buccal route; the sublinqual route; the epidural route; the spinal route; the anal route; and the intracranial route.

23. (Currently Amended) The method according to claim 22, wherein the effective amount is between 0.5 μg and 2,000 μg of the OPGL polypeptide~~, the subsequence thereof or the~~ analogue ~~thereof~~.

24. (Currently Amended) The method according to claim 22~~ or 23~~, wherein the OPGL polypeptide ~~or~~ analogue is contained in a virtual lymph node (VLN) device.

25. (Cancelled).

26. (Cancelled).

27. (Cancelled).

28. (Currently Amended) The method according to ~~any one of claims 22-27~~claim 22, which includes at least one administration/introduction per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations/introductions.

29. (Cancelled).

30. (Cancelled).

31. (Cancelled).

32. (Cancelled).

33. (Cancelled).

34. (Cancelled).

35. (Cancelled).

36. (Cancelled).
37. (Cancelled).
38. (Cancelled).
39. (Cancelled).
40. (Cancelled).
41. (Cancelled).
42. (Cancelled).
43. (Cancelled).
44. (Cancelled).
45. (Cancelled).
46. (Cancelled).
47. (Cancelled).
48. (Cancelled).
49. (Cancelled).
50. (Cancelled).
51. (Cancelled).
52. (Cancelled).
53. (Cancelled).
54. (Cancelled).
55. (Cancelled).
56. (Cancelled).
57. (Newly Presented) The method according to claim 1, wherein the animal is a human being.
58. (Newly Presented) The method according to claim 12, wherein the Tetanus toxoid epitope is a P2 or P30 epitope.